"When Roscius Was an Actor in Rome–" Care for the Elderly with N2-Positive Non–Small-Cell Lung Cancer

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Polonius: *The best actors in the world, either for Tragedie, Comedie, Historie, Pastorall: Pastoricall-Comicall-Historicall-Pastorall: Tragical-Historical: Tragicall-Comical-Historicall-Pastorall: Scene indivible, or Poem unlimited. Seneca cannot be too heavy, nor Plautus too light, for the law of Writ, and the Liberty. These are the only men.*[1]

The problem of stage III non–small-cell lung cancer (NSCLC) is one of the most interesting in all of thoracic oncology. The issues arise from the relative inaccessibility of the mediastinum to biopsy,[2,3] the great heterogeneity of the population (ranging from patients with T3N1M0, through those with T1–3N2M0, and since the American Joint Committee on Cancer 7th edition system, patients with T4N0–1M0 disease),[4] and the diversity of potential treatment options.[5] Even within the more homogeneous group, those with stage IIIA on the basis of N2 disease, there remains great heterogeneity because of the range of T-categories included, and differences in the amount of N2 disease.[6]

At one extreme, patients with unexpected N2 disease that is detectable only after pathology examination of the resection specimen, after false-negative standard preoperative staging tests, have a prognosis very different from those with bulky multi-station lymphadenopathy, who reside at the other end of the spectrum.[6,7] Matters are further complicated by the varying levels of histologic confirmation of N2 disease in the clinical trials in this population. Therefore, interpreting clinical trials of N2 NSCLC demands careful attention to the population selected by the eligibility criteria, and the final results always seem to pose more questions than they answer.

And clinical trials there have been. In the past three decades, at least seven major prospective, randomized multi-institutional trials and two meta-analyses have attempted to shed light on questions that swirl around the optimal treatment of N2 NSCLC. In the 1990s, Rosell et al.[8] and Roth et al.[9] independently demonstrated that the combination of preoperative chemotherapy and surgery (Polonius might say, "tragical-historical") was superior to surgery alone; Dillman et al.[10] demonstrated that the combination of chemotherapy and radiation (historical-pastoral?) was superior to radiation alone for patients who could not undergo surgery; and Furuse et al.[11] reported the superiority of concurrent combined modality chemoradiotherapy over sequential therapy. In the next decade, the International Adjuvant Lung Trialists[12] and the Lung Adjuvant Cisplatin Evaluation meta-analysis[13] demonstrated that postoperative adjuvant chemotherapy improves survival of patients with N2 disease; and an update Postoperative Radiation Therapy meta-analysis remained ambivalent about the value of postoperative adjuvant radiation therapy in patients with N2 disease.[14] The unifying theme of these studies was the superiority of multimodal therapy over unimodal therapy in patients who are fit for such treatment ("Scene indivible" indeed!).

The question of the optimal multimodal therapy has been addressed by two major randomized controlled trials. Van Meerbeeck et al.[15] compared outcomes in patients who were randomized, after induction chemotherapy, to either definitive radiation therapy or surgery, and found no difference in survival. However, an unplanned analysis of the

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resection cohort suggested that patients with complete resection short of pneumonectomy, and clearance of N2 disease after induction chemotherapy, might benefit more from surgery.[15] Unfortunately, 47% of patients in this study received pneumonectomy, including 25% on the right side. Albain et al.[16] compared the outcomes of recipients of concurrent chemoradiotherapy, who were randomized to surgery (tragical-comical-historical-pastoral) or no surgery and found no difference in survival between the two arms, suggesting that the addition of surgery to chemoradiation therapy provides no additive benefit. However, in an unplanned exploratory matched subset analysis of trimodal versus bimodal therapy, in which recipients of lobectomy were analyzed separately from those who received pneumonectomy, survival was significantly superior with trimodality therapy using lobectomy, whereas, it was significantly inferior when pneumonectomy was the surgical option used for trimodality therapy.

These studies raise several interesting questions: "Is trimodality therapy the best treatment when the surgeon is sure he will not have to resort to pneumonectomy?," "Is the addition of surgery preferable in patients with clearance of mediastinal lymph node disease?," and, "Would trimodality therapy be better in carefully selected patients at centers with low postpneumonectomy mortality?"[17] These questions cannot be answered with current evidence, they are subject to personal belief, institutional bias, and midrashic interpretation of the data.

Against this background, we come to the original submission by Berry et al.,[18] which gives a retrospective review of all resections for N2-positive NSCLC in the U.S. Surveillance, Epidemiology, and End Results program (SEER)-Medicare database, a linkage of directly abstracted cancer registry data (SEER) with coded payment records from Medicare, a U.S. national health care payer that predominantly covers U.S. residents aged 65 years and above, and useful in providing information on practice patterns and outcomes in the elderly.[19] The authors' stated objectives were to examine the pattern of care for IIIA (N2) NSCLC in the elderly, and to test the hypothesis that nonclinical characteristics play an important role in the use of surgery.

To address these objectives, they reviewed 2958 eligible patients in the SEER-Medicare database, who received resections from 2004 to 2007. They found a heterogeneity of treatments: 52% had combined modality therapy, 30% had unimodal therapy, 18% had no treatment; 73% had some sort of definitive local therapy (radiation or surgery) in combination or unimodal fashion. Somewhat surprisingly (for this era, given the state of the data at the time), 13% received radiation therapy only, 9% had chemotherapy alone, and 7% had trimodality therapy. The factors most strongly associated with the choice of surgery were predictable—age and T-category. Examination of their hypothesis about the impact of nonclinical characteristics on the use of surgery, revealed sex and socioeconomic status (median residential income) as unexpected, albeit weak, associated factors.

The study by Berry et al.[18] is interesting because the information about patterns of care can serve as a useful foundation on which to construct future examinations of the evolution of practice patterns in the wake of the seven landmark trials and two meta-analyses cited.[8–16] There is much that is reassuring in their findings, but also much to be disturbed by. On the positive side, it is encouraging that the clinicians seemed to have acted appropriately with the evidence before them. Majority use of multimodality therapy is encouraging, as is the seeming tendency to triage for or against surgery on the basis of appropriate clinical factors.

Although the authors raise the issue of racial and socioeconomic disparities in the choice of surgery, there is not much in this particular analysis to go on, at least by their multivariate analysis, which suggests rather, that the nonclinical factors are probably linked and of marginal impact. No surprise here, given that the impact of demographics on health care disparities would have been significantly dispersed by the selection criteria—these patients by definition had health insurance (Medicare). The apparently higher survival rate of patients who had surgery most likely indicates that factors (advanced age, limited pulmonary function, poor overall performance status, more extensive tumors, etc.) militating against surgery, also drove the higher mortality of the nonsurgery patients. More reliable evidence from the randomized controlled trials cited above must temper any suggestions in this report of a clear superiority of surgery.

The most disturbing aspects of this report come from the pattern-of-care analysis. Eighteen percent of patients received no treatment, 30% received unimodal care, and 40% to 48% (give or take the 8% who had surgery only) received no attempt at curative therapy. Is this evidence of the frail condition of these patients, a sense of nihilism about the value of treating patients with lung cancer, the usual delay of evidence dissemination and implementation (the Roth, Rossell, and Dillman studies all having been published in high-profile journals in the 1990s; the current study cohort was treated in the 21st century), or is it some other factor? The same range of concerns applies to the infrequent use of invasive staging tests to confirm N2 disease, especially given the prior report of Farjah et al.[20,21] working on this same population, but in a partially overlapping era.

Lung cancer care is emerging from the dark ages into a period of light. The advent of screening, minimally invasive means of accessing the mediastinum to improve clinical nodal staging, minimally invasive surgical resection techniques that limit the morbidity of surgery, thereby expanding the candidate population, improvements in supportive care for recipients of multimodality therapy, and the incoming cascade of targeted therapies augur well for the future. We must not, like Prince Hamlet, "defy augury." We must communicate our sense of optimism to the greater community to increase use of curative-intent therapy. The study by Berry et al.[18] will serve as a useful template for future trend analyses of the pattern of care. As knowledge of the value of multimodality management expands, we hope to see a trend toward more assertive use of multimodality staging and treatment for this most fascinating subset of patients who are *frighted* with the peril of mortality, yet sustain a real potential for cure.

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